



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/06, 9/10, 31/00	A3	(11) International Publication Number: WO 99/02133 (43) International Publication Date: 21 January 1999 (21.01.99)
(21) International Application Number: PCT/EP98/05046 (22) International Filing Date: 8 July 1998 (08.07.98) (30) Priority Data: 97202096.0 8 July 1997 (08.07.97) EP (71) Applicant (for all designated States except US): GIST-BROCADES B.V. [NL/NL]; Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): LEFEVRE, Jean-Marie [FR/FR]; 30, rue des Trois Cailloux, F-80000 Amiens (FR). EDENS, Luppó [NL/NL]; Hoflaan 118, NL-3062 JL Rotterdam (NL). (74) Agents: SWINKELS, Bart, Willem et al.; Gist-Brocades B.V., Patents and Trademarks Dept., Wateringseweg 1, P.O. Box 1, NL-2600 MA DELFT (NL).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 1 April 1999 (01.04.99)
(54) Title: TOPICAL APPLICATION OF A COMBINATION OF BENZOYL PEROXIDE AND A SECOND ACTIVE INGREDIENT (57) Abstract <p>The present invention discloses a multicompartment dispensing system separately containing a first composition comprising benzoyl peroxide and a second composition comprising a second active ingredient, preferably an antimicrobial agent. Said first and second composition generate a final composition when mixed upon dispensing, said final composition being effective to apply an effective combination of benzoyl peroxide and said second active ingredient.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/EP 98/05046

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/06 A61K9/10 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 2 015 111 A (WOO ET AL.) 23 October 1991 see page 6, line 10 - page 7, line 1 see claims 1,4,5,11-13,72-79 ---	1-7
Y	GB 2 088 717 A (RORER INTERNATIONAL) 16 June 1982 see the whole document ---	1-7
Y	WO 93 15726 A (BAROODY ET AL.) 19 August 1993 see page 7, line 9 - page 11, line 16 ---	1-7
Y	US 5 538 732 A (SMITH ET AL.) 23 July 1996 see column 5, line 18 - line 21 see claims 1-29 --- -/--	1-7

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

21 December 1998

Date of mailing of the international search report

14/01/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

Int. l. Application No

PCT/EP 98/05046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 11680 A (SCHERING AKTIENGESELLSCHAFT) 3 April 1997 see claims 1,6,7,14,15 ---	1-7
P,Y	WO 97 27841 A (GIST-BROCADES B.V.) 7 August 1997 cited in the application see page 9, line 1 - page 10, line 14 -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. :lonal Application No

PCT/EP 98/05046

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
CA 2015111	A	23-10-1991	NONE	
GB 2088717	A	16-06-1982	AR 229405 A	15-08-1983
			AT 381452 B	27-10-1986
			AT 285581 A	15-03-1986
			AU 557147 B	11-12-1986
			AU 7202981 A	17-06-1982
			BE 889327 A	16-10-1981
			CA 1179599 A	18-12-1984
			CH 656307 A	30-06-1986
			CH 647147 A	15-01-1985
			DE 3124698 A	08-07-1982
			DK 273981 A	09-09-1982
			FR 2495471 A	11-06-1982
			GB 2090135 A	07-07-1982
			IE 52227 B	19-08-1987
			JP 57099525 A	21-06-1982
			MX 9203750 A	01-09-1992
			NL 8102997 A	01-07-1982
			SE 8103925 A	09-06-1982
			US 4497794 A	05-02-1985
			US 4692329 A	08-09-1987
			ZA 8104215 A	23-02-1983
WO 9315726	A	19-08-1993	AU 3478893 A	03-09-1993
			BR 9305884 A	19-08-1997
			CA 2130341 A,C	19-08-1993
			CN 1077887 A	03-11-1993
			EP 0626844 A	07-12-1994
			FI 943783 A	17-08-1994
			JP 7504168 T	11-05-1995
			MX 9300848 A	31-08-1994
			NO 943045 A	17-08-1994
			NZ 249021 A	27-08-1996
			PL 171127 B	28-03-1997
			SG 48195 A	17-04-1998
			US 5733886 A	31-03-1998
US 5538732	A	23-07-1996	NONE	
WO 9711680	A	03-04-1997	AU 7282796 A	17-04-1997
			CA 2232621 A	03-04-1997
			EP 0854705 A	29-07-1998
			NO 981412 A	12-05-1998
			PL 325978 A	17-08-1998
WO 9727841	A	07-08-1997	AU 1721697 A	22-08-1997
			BR 9702049 A	13-01-1998
			CA 2216169 A	07-08-1997
			EP 0817613 A	14-01-1998



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/08, 9/10, 31/00	A2	(11) International Publication Number: WO 99/02133 (43) International Publication Date: 21 January 1999 (21.01.99)
(21) International Application Number: PCT/EP98/05046 (22) International Filing Date: 8 July 1998 (08.07.98) (30) Priority Data: 97202096.0 8 July 1997 (08.07.97) EP (71) Applicant (for all designated States except US): GIST-BROCADES B.V. [NL/NL]; Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): LEFEVRE, Jean-Marie [FR/FR]; 30, rue des Trois Cailloux, F-80000 Amiens (FR). EDENS, Luppó [NL/NL]; Hoflaan 118, NL-3062 JL Rotterdam (NL). (74) Agents: SWINKELS, Bart, Willem et al.; Gist-Brocades B.V., Patents and Trademarks Dept., Wateringseweg 1, P.O. Box 1, NL-2600 MA DELFT (NL).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: TOPICAL APPLICATION OF A COMBINATION OF BENZOYL PEROXIDE AND A SECOND ACTIVE INGREDIENT (57) Abstract <p>The present invention discloses a multicompartment dispensing system separately containing a first composition comprising benzoyl peroxide and a second composition comprising a second active ingredient, preferably an antimicrobial agent. Said first and second composition generate a final composition when mixed upon dispensing, said final composition being effective to apply an effective combination of benzoyl peroxide and said second active ingredient.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Topical application of a combination of benzoyl peroxide
and a second active ingredient

5

Field of the invention

The present invention relates to the field of topical application of a combination of incompatible active ingredients, one being benzoyl peroxide.

Background of the invention

Acne vulgaris is a skin disorder frequently occurring in young people. It is a disorder of the sebaceous follicles and is associated with the sharp increase in androgen production during adolescence. Hyperproduction of sebum and inflammation caused by proliferation of *Propionibacterium* *acne* are associated with this skin disorder.

Erythromycin, or a mixture of erythromycin and clindamycin, is commonly used for the treatment of acne. However, propionibacterial resistance to these antibiotics is a growing concern because of its high incidence (Eady et al. (1993), Br. Med. J. 306: 555-556), the resistance to high concentrations of erythromycin and the cross resistance to clindamycin (Eady et al. (1989), Br. J. Dermatol. 121: 51-57). One way to minimize the selective pressure towards resistancies is to combine the antibiotic with benzoyl peroxide.

Benzoyl peroxide is clinically effective because of its bactericidal activity against *Propionibacterium acnes* as well as through its mild keratinolytic effect.

Unfortunately, several factors hamper the development of convenient topical formulations containing both erythromycin as well as benzoylperoxide.

For example, erythromycin can be stably formulated only in high concentrations of suitable solvents such as ethanol (Brisaert et al. (1996), Pharm. World Sci. 18: 182-186), whereas stability in formulations containing high levels of water is unacceptably low. However, topical

application of high concentrations of ethanol is undesirable because of its irritancy to the skin.

In contrast, the stability of benzoyl peroxide in solvents like ethanol is low. Long term stability of benzoyl peroxide can only be guaranteed in compositions providing a low benzoyl peroxide solubility (Chellquist and Gorman (1992), Pharm. Res. 9: 1341-1346). In addition, benzoyl peroxide is extremely reactive, because of instability of the O-O bond. Consequently, benzoyl peroxide can be expected to have a deleterious effect on the chemical stability of other compounds mixed with benzoyl peroxide.

Currently, for topical application of a combination of benzoyl peroxide and erythromycin, a suitable solvent has to be added to both compounds being individually packed as a powder, whereupon the resulting solution in turn has to be mixed into a topical gel. It is highly desirable to avail of a less cumbersome method to apply these compounds.

Description of the invention

20

The present invention provides a convenient solution to the above problems by applying a multicompartment dispensing system to enable separate containment of individual compositions, i.e. a first composition comprising benzoyl peroxide and a second composition comprising a second active ingredient. According to the invention, said first and second composition generate a final composition when mixed upon delivery, said final composition being effective to apply benzoyl peroxide as well as the second active ingredient in an effective form. The mixing of the individual compositions thereby may occur either *in situ* or in the dispensing system prior to delivery.

The present invention further discloses a method to produce an effective composition comprising benzoyl peroxide and a second active ingredient by *in situ* mixing of two individual compositions, each comprising a predetermined amount of either benzoyl peroxide or a second active ingredient.

The use of a multicompartment dispensing system according to the invention enables the preparation and use of separate compositions, on the one hand a composition comprising benzoyl peroxide as the active ingredient and on the other hand a composition comprising a second active ingredient. These separate compositions are prepared in such a way that the individual requirements for stable formulation of each active ingredient are fulfilled. In addition, the separate compositions are prepared in such a way that the final composition is effective to deliver the active ingredients present in each individual composition in a form suitable and effective for direct application.

Thus, the nature of the first and second composition are determined by on the one hand the stability requirements of each individual active ingredient and on the other hand the desired properties of the final composition.

The second active ingredient is an ingredient which may act in concert with or even synergistically with benzoyl peroxide. Said second active ingredient for instance may be an antimicrobial agent, preferably an antibacterial or antifungal agent. More preferably, said antimicrobial agent is a macrolide antibiotic, such as erythromycin or natamycin, and/or an aminoglycoside antibiotic, such as clindamycin or lincomycin. Another example of an antimicrobial agent which may be combined with benzoyl peroxide is a sphingoid base, like sphingosine or phytosphingosine (Bibel et, al (1992), J. Invest, Dermatol. 98: 269-273).

Typically, a stable composition may be obtained when an active ingredient is formulated as a suspension formulation, e.g. a composition wherein the vehicle is selected to provide a low solubility of the active ingredient. Sedimentation of a suspended active ingredient in a suspension formulation is prevented by the use of a suitable viscosifying or thickening agent. A stable composition of the active ingredient further may be obtained using a high concentration of a non-aqueous solvent in said composition. Examples of such non-aqueous solvents are ethanol or hydric solvents like polyethylene glycol,

butylene glycol, propylene glycol or glycerol. A stable composition of the active ingredient further may be obtained by dissolving a high concentration of the active ingredient in the solvent of choice.

5 The viscosity of the individual compositions is adjusted to the desired level using a viscosifying or thickening agent. The concentration of the viscosifying agent used mainly is determined by the solvent, the pH, and the weight and size of the particles to be kept in
10 suspension. Conveniently, the concentration of the viscosifying agent may range from 0.1-3%. Desirable viscosities may range from 100 to 30.000 cps (Brookfield, 25 °C - 25 rpm), preferably from 1000 to 10.000 cps. It is preferred that the two individual compositions present in
15 the dispenser according to the invention have a substantially similar viscosity.

 Examples of viscosifying agents for gellifying an aqueous suspension composition include Carbomer viscosifiers like Carbopol 940 (B.F. Goodrich) and cellulose derivatives
20 like hydroxypropylmethylcellulose, optionally in combination with colloidal magnesium silicate (Veegum). To stabilize suspensions containing particles and/or containing high concentrations of ethanol or hydric solvents like polyethylene glycol, butylene glycol, propylene glycol or
25 glycerol, viscosifying agents which may be considered include xanthans, Carbomer viscosifiers like Carbopol Ultrez 10 or carrageenans like Satia gum UTC 30 (SBI, Benelux).

 The concentration of the active ingredient in the stable composition typically depends on both the desired end
30 concentration of said active ingredient in the final composition as well as on the ratio wherein the first and second composition are mixed to obtain the final composition.

 The ratio in which the two individual compositions are
35 delivered by the dispensing system can be adjusted as desired. Typically, said ratio may be adjusted to any value within a range varying from 1:1 to 1:50. Preferably, said ratio may vary from 1:2 to 1:20.

To obtain a dilution of one composition into the other is especially advantageous in the case that one composition contains a solvent in a concentration which is too high for direct topical application.

5 A suitable benzoyl peroxide composition for use in the dispensing system according to the invention is for instance an aqueous suspension formulation comprising benzoyl peroxide in a concentration ranging from 2 to 30 % (w/v).

Suitable formulations guaranteeing long term stability
10 of benzoyl peroxide compositions at elevated temperature conditions are given by e.g. Chellquist and Gorman (*supra*) and Bollinger et al. (J. Pharm. Sci. 66 (1977): 718-722).

Typically, end concentrations of benzoyl peroxide on the skin may range from 2% to 15%.

15 The nature of the composition comprising the second active ingredient will depend on the requirements for stable formulation of the second active ingredient.

Stable erythromycin compositions are for instance specified by Vandebossche et al. (Int. J. Pharmaceutics, 67
20 (1991): 195-199). For long term stability at elevated temperatures erythromycin compositions containing high levels of ethanol are preferable (Brisaert et al. (1994), Farmaceutisch Tijdschrift voor België, 1-2, 2-5). The use of pure ethanol as a solvent for erythromycin is also
25 advantageous because erythromycin base can be dissolved in concentrations up to 30%. Alternatively, stable erythromycin compositions are suspension formulations of erythromycin, suspended in for instance propylene glycol, PEG 400, isopropanol, or mixtures thereof.

30 Stable aqueous natamycin compositions are described for instance in European Patent Application EP 678241. The stable natamycin compositions disclosed in EP 678241 are suspensions of natamycin crystals in an aqueous medium, wherein sedimentation of the crystals is prevented by the
35 addition of a suitable viscosifying agent, such as xanthan or carrageenan. Additional suitable viscosifiers include Carbomers or related resins.

Stable aqueous clindamycin compositions are for instance specified by Oesterling (J. Pharm. Sciences (1970)

59: 63-67). Using clindamycin, maximum stability is obtained at a pH value of 3-5.

The nature of the final composition further may determine additional properties of one or both individual composition(s). For instance, the pH of the benzoyl peroxide composition and/or the composition comprising the second active ingredient may be adjusted to the desired pH value of the final composition.

In a preferred embodiment of the invention, a multicompartment dispenser is provided containing a first composition comprising benzoyl peroxide and a second composition comprising erythromycin. Said first composition comprises 5% (w/v) benzoyl peroxide suspended in an aqueous composition adjusted with sodium hydroxide to a pH of 8 - 8.5 and comprising Carbopol 940 as a viscosifying agent to reach a Brookfield viscosity between 500 and 5000 cps. Said second composition comprises 30% (w/v) erythromycin dissolved in 96% ethanol and Carbopol Ultrez 10 as a viscosifier. Preferably, the viscosity of the erythromycin composition is comparable to the viscosity of the benzoyl peroxide gel. Said first and second composition are mixed in a ratio of nine parts first to one part second composition, resulting in a final composition having a concentration of about 5% benzoyl peroxide and 3% erythromycin. In this embodiment, the nature of the erythromycin composition, i.e. dissolved in 96% ethanol, specifically requires a delivery ratio of both compositions which ensures a dilution of said erythromycin composition in the final composition of at least about a factor 10.

Since erythromycin is more active at an alkaline pH (Heilman and Herrell (1952), Proc. Staff Meetings Mayo Clinic 27: 285-304), the adjustment of the pH to a value of about 8.5 is desirable for optimal activity. However, this pH value has a deleterious effect on erythromycin stability. The use of a dispenser according to the invention ensures that this pH adjustment occurs only after delivery from the dispenser and mixing on the skin, whereby the final pH is brought about by the benzoyl peroxide composition.

In a further embodiment of the invention, the second composition comprises natamycin as the active ingredient.

The solubility of natamycin, and thus its antifungal effectiveness, is optimal in the higher or lower pH ranges, e.g. around pH 3. Contrary, its stability in these pH ranges is rather low. Therefore, the use of a dispenser according to the invention allows for the combination of a concentrated stable natamycin composition with a stable but acidic benzoyl peroxide composition.

The dispensing system used is not critical to the invention. The present invention contemplates any dispensing system which allows for a separate containment as well as a simultaneous dosing (dispensing) of the individual compositions. Examples of suitable dispensing systems are given in WO 97/27841. A preferred multicompartment dispensing system is a dispenser containing two differently-sized compartments. Such a dispenser enables the dispensing of unequal amounts of two different compositions.

Care should be taken to use metal parts which are teflon-coated or nylon-coated (Rilsan process), since benzoyl peroxide is a rather corrosive compound.

The dispensing system according to the invention provides a convenient way to topically deliver a combination of benzoyl peroxide and a second active ingredient.

Example 1

Topical application of benzoyl peroxide and erythromycin

Benzamycin® is a pharmaceutical product marketed by Dermik (USA) against serious forms of acne. The product consists of a mixture of 3% erythromycin and 5% benzoyl peroxide. Owing to the chemical incompatibility of erythromycin and benzoyl peroxide, the product comes as two separate jars, one containing erythromycin and one containing a benzoyl peroxide gel. Prior to use, erythromycin and benzoyl peroxide have to be mixed and refrigerated to allow a maximal use period of 3 months by the patient.

A two chamber dispenser was supplied by CosmoCair (Gist-brocades, Delft, the Netherlands). This "Symbio" dispenser combines in one housing a normal and an air-free lotion pump, both activated by the same actuator. Each one of the two pumps is connected to its own individual chamber. The air-free lotion pump is connected with a small cartridge equipped with a plunger in the bottom of the cartridge. The other pump is connected with a diptube and dispenses the formulation from the largest chamber. When the dispenser is assembled, the filled cartridge is (partly) submerged in the formulation contained in the largest chamber. During storage and use, the formulations contained in the cartridge and the largest chamber are kept completely separated.

Upon actuation, the dispenser delivers 0.4 grams of formulation, approx. 0.36 ml from the largest chamber and 0.04 ml from the cartridge. Both product streams are kept completely separated until they are ejected from the orifices of the dispenser.

To mimic Benzamycin® in terms of final concentrations of benzoyl peroxide and erythromycin on the skin, stable formulations of benzoyl peroxide and erythromycin were used to fill the two compartments of the Symbio dispenser.

To prepare a slightly viscous suspension of benzoyl peroxide, 2.0 grams of Carbopol Ultrez 10 (B.F. Goodrich) was carefully added to 450 ml of water. Subsequently 60 grams of acetone were added as well as 43.7 grams of benzoyl peroxide (Genfarma, the Netherlands). Using 8N NaOH, the pH of the solution was raised to pH 8.0 and water was added to obtain a final volume of 600 grams. Finally the suspension was homogenized with an Ultra-turrax. The next morning the suspension was centrifugated for 10 minutes at 5000 rpm in a Sorvall centrifuge to remove any air bubbles, if necessary carefully homogenized again and filled in the largest chamber of the dispenser.

To prepare a 10-times concentrated solution of erythromycin, 20 grams butylene glycol, 1.0 grams Carbopol Ultrez 10 and 49 grams of absolute ethanol were added to a glass beaker. Subsequently 30 grams of erythromycin (Genfarma, the Netherlands) was added and the mixture was

mixed at 40 °C until a clear solution was obtained. Finally this solution was centrifuged to remove any air bubbles and filled into a cartridge. To close the cartridge, the plastic plunger was applied in such a way that no residual air was
5 left between the erythromycin concentrate and the plunger.

After attachment of the filled cartridge to the airfree micropump and assembly of the pumphead with the benzoyl peroxide filled container, the pump was primed to prepare for dispensing of the two formulations on the skin.
10 Manual mixing of the erythromycin concentrate with the co-dispensed benzoyl peroxide on the skin yielded a mixture containing 3% erythromycin and 5% benzoyl peroxide.

Claims

1. A multicompartment dispensing system separately containing a first composition comprising benzoyl peroxide
5 and a second composition comprising a second active ingredient, said first and second composition generating a final composition when mixed upon dispensing, and said final composition being effective to apply a combination of benzoyl peroxide and said second active ingredient.
- 10 2. The dispensing system of claim 1, wherein the benzoyl peroxide composition is an aqueous suspension formulation, further comprising a viscosifying agent.
- 15 3. The dispensing system of claim 1 or 2, wherein the second active ingredient is an antimicrobial agent.
4. The dispensing system of claim 3 wherein the antimicrobial agent is a macrolide and/or an aminoglycoside
20 antibiotic.
5. The dispensing system of claim 4, wherein the macrolide antibiotic is erythromycin or natamycin.
- 25 6. The dispensing system of claim 5, wherein the erythromycin composition is a solution of erythromycin in ethanol, further comprising a suitable viscosifying agent.
7. A method to produce an effective composition
30 comprising benzoyl peroxide and a second active ingredient by *in situ* mixing of two individual compositions, each comprising a predetermined amount of either benzoyl peroxide or said second active ingredient.